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ORIGINAL ARTICLE

Semen Analysis

Effect of SARS-CoV-2 infection on semen parameters in sperm bank volunteers with normal sperm concentration

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In this study, we aimed to assess the effect of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on semen parameters. The study comprised 110 sperm volunteers who self-reported SARS-CoV-2 infection from the Human Sperm Bank of the Center for Reproductive Medicine, Shandong University (Jinan, China). The volunteers had normal sperm concentration before infection. Each volunteer provided semen samples before and after infection. We selected 90 days after infection as the cutoff point. Semen parameters within 90 days after infection of 109 volunteers (group A) were compared with semen parameters before infection. Moreover, semen parameters on or after 90 days after infection of 36 volunteers (group B) were compared with semen parameters before infection. Furthermore, based on whether the volunteers had completed the three-dose SARS-CoV-2 vaccination booster, volunteers in group A and B were further divided into two subgroups separately. Semen parameters were compared before and after infection in each subgroup. Our results showed that in this cohort population, the semen quality in volunteers with normal sperm concentrations before infection decreased after SARS-CoV-2 infection within 90 days, while the semen quality returned to preinfection levels after 90 days. The completion of a three-dose SARS-CoV-2 vaccination booster may exert a protective effect on semen quality after infection.
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Keywords: SARS-CoV-2; SARS-CoV-2 vaccination; semen quality; sperm donation; sperm parameters

INTRODUCTION

Three years have passed since the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first discovered in 2019.[1] The effect of SARS-CoV-2 infection on semen parameters was investigated, with varying results.[2–9] Although some studies reported a significant decrease in sperm concentration, motility, and morphology,[2,4–9] others did not find significant changes in semen parameters in men with SARS-CoV-2 infection.[3,10] A few studies have assessed the changes in semen parameters after SARS-CoV-2 infection in Chinese men, but the comparison data of semen parameters before and after infection in the same cohort have not been reported. In addition, whether SARS-CoV-2 vaccine in China has a protective effect on male semen quality has also not yet been reported.

Therefore, the present study aimed to assess the effect of SARS-CoV-2 infection on sperm parameters in volunteers who had experienced this infection. We also evaluated whether SARS-CoV-2 vaccine exerts a protective effect on semen quality.

PARTICIPANTS AND METHODS

The study was a single-center retrospective study. The cohort comprised 110 sperm volunteers who self-reported SARS-CoV-2 infection from the Human Sperm Bank of Center for Reproductive Medicine, Shandong University (Jinan, China). The volunteers had normal sperm concentration before infection. From February 6, 2022, to April 21, 2023, they visited the sperm bank both before and after SARS-CoV-2 infection. A total of 102 volunteers had received at least one dose of coronavirus disease (COVID-19) vaccine, and 86 had completed a three-dose SARS-CoV-2 vaccination booster. All the participants self-reported SARS-CoV-2 infection and provided the specific dates of the first symptoms of the disease. Each volunteer had donated at least one semen sample within one year before and at least one sample after SARS-CoV-2 infection.

Semen analysis was performed by the trained professional staff of the Human Sperm Bank following the recommendations of the World Health Organization (WHO) Laboratory Manual for the Examination and Processing of Human Semen (5th edition).[11] Semen volume, sperm concentration, progressive motility (PR), and motility (PR+nonprogressive motility [NP]) were recorded, and total progressive motility sperm count (TPRSC) and total sperm count (TSC) were calculated for each sample.

Since the spermatogenic cycle in humans is estimated to be approximately 74 days,[12,13] based on the previous literature,[14,15] and

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considering epididymal transport that lasts approximately 16 days, we selected 90 days as the cutoff point of the observation. Group A consisted of 109 volunteers who provided at least one sample within 90 days after infection. We selected the first sample provided after infection for the study of group A. Group B consisted of 36 volunteers who provided at least one sample on or after 90 days after infection. We selected the first sample provided on or after 90 days for the study. If a volunteer had multiple records of semen analysis at various intervals, he was assigned to the appropriate groups for counting. A volunteer within a group was included only once. There were 35 volunteers in both groups A and B. Hence, there were 110 volunteers but 145 postinfection samples in this study. Based on whether the volunteers had completed the three-dose SARS-CoV-2 vaccination booster, group A was divided into two subgroups (group C [completed; $n = 86$] and group D [uncompleted; $n = 23$]) and group B was further divided into subgroups (group E [completed; $n = 28$] and group F [uncompleted; $n = 8$]). The sperm parameters were compared before and after infection in each group.

This study was approved by the Institutional Review Ethics Board (IRB) of the Center for Reproductive Medicine, Shandong University (Approval No. IRB 2023-30). All volunteers signed informed consent during their first visit to the human sperm bank, agreeing that their semen samples and data could be used for research.

Descriptive statistical results are presented as nontransformed data. Since the distributions of the analyzed parameters were nonnormal, the percentiles and medians were calculated. The data were summarized using medians and interquartile ranges (IQRs). Wilcoxon rank-sum test was used to compare the semen parameters before and after infection. Statistical analysis was carried out using SPSS Statistics Version 22.0 Release 2013 (IBM SPSS Statistics for Windows, IBM, Armonk, NY, USA). A two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

Among those who visited the human sperm bank between February 6, 2022, and April 21, 2023, a total of 110 volunteers visited both before and after SARS-CoV-2 infection and all of them had normal sperm concentration before infection. The general characteristics of the 110 volunteers in each group are summarized in **Table 1**.

Table 2 shows the semen parameters before and after SARS-CoV-2 infection in groups A and B. In group A, sperm concentration, PR, PR+NP, TPRSC, and TSC decreased after infection compared to that before infection (39.0×10^6 ml^{-1} *vs* 50.0×10^6 ml^{-1}, 37.0% *vs* 44.0%, 46.0% *vs* 56.0%, 36.5×10^6 *vs* 56.7×10^6, and 111.0×10^6 *vs* 148.8×10^6, respectively). Significant differences were detected in sperm concentration, PR, PR+NP and TPRSC ($P = 0.015$, 0.027, 0.031, and 0.035, respectively) before and after infection in group A. Strikingly, group B did not show statistical differences in sperm concentration, PR, PR+NP, TPRSC, and TSC ($P = 0.291$, 0.065, 0.061, 0.136, and 0.153, respectively) before and after infection.

Table 1: Descriptive characteristics of the participants

Characteristic	*Group A (n=109), median (IQR)*	*Group B (n=36), median (IQR)*
Age (year)	23.0 (22.0–28.0)	23.0 (22.0–27.0)
BMI (kg m^{-2})	23.6 (22.0–26.7)	23.1 (22.0–25.9)
Time since last donation before infection (day)	29.0 (21.0–42.0)	28.0 (20.0–36.0)
Time from infection to first donation after infection (day)	29.0 (16.5–60.0)	93.0 (91.0–96.0)
Interval between two sperm donations (day)	70.0 (46.0–99.5)	122.0 (117.0–131.5)

Group A: volunteers who had semen analysis data within 90 days after SARS-CoV-2 infection; group B: volunteers who had semen analysis data on or after 90 days after SARS-CoV-2 infection. BMI: body mass index; IQR: interquartile range; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

Table 3 shows the semen parameters before and after SARS-CoV-2 infection in groups C and D. In group C, no significant differences were observed in sperm concentration, PR, PR+NP, TPRSC, and TSC ($P = 0.081$, 0.138, 0.107, 0.123, and 0.139, respectively) before and after infection, while in group D, sperm concentration and PR decreased significantly after infection ($P = 0.048$ and 0.046, respectively).

Table 4 shows the semen parameters before and after SARS-CoV-2 infection in groups E and F. No significant differences were observed in sperm concentration, PR, PR+NP, TPRSC, and TSC ($P = 0.589$, 0.157, 0.104, 0.339, and 0.412, respectively, in group E; and $P = 0.161$, 0.206, 0.263, 0.208, and 0.207, respectively, in group F) before and after infection.

DISCUSSION

This study was designed to assess the effect of SARS-CoV-2 infection on sperm parameters in volunteers with normal sperm concentrations who had experienced the infection. The results showed that sperm concentration, PR, PR+NP, and TPRSC decreased within 90 days after the infection and differed significantly from preinfection. Furthermore, no statistical differences were observed in sperm parameters before and after infection in group B (≥90 days). These findings indicated that semen quality decreased after SARS-CoV-2 infection but returned to preinfection levels after 90 days. Furthermore, the completion of the SARS-CoV-2 three-dose booster vaccination had a protective effect on semen quality.

The current study showed that medians of all semen parameters (except semen volume) were higher 90 days after infection than before. The underlying reason may be that the participants in this study were infected during the same period (December 2022). The time point of 90 days after infection was spring, when the medians of semen parameters were slightly higher than those in winter (pre-infection); this phenomenon was consistent with the results of previous studies.[16,17]

Some studies reported a significant decrease in sperm concentration, motility, and morphology, while others did not detect significant changes in semen parameters in men with SARS-CoV-2 infection. In a multicenter study, Erbay *et al.*[6] observed significant differences in sperm motility and vitality in mildly symptomatic patients and all sperm parameters in moderate symptomatic patients after COVID-19 compared to those in individuals before infection. Best *et al.*[7] found that the sperm concentration and TSC were lower in men infected with COVID-19 than in those who tested negative. One study reported that the patients hospitalized with COVID-19 had significantly lower sperm concentrations compared to age-matched control males, while 9 of twenty-three COVID-19 inpatients had oligospermia.[18] Another study showed that semen volume, sperm motility, progressive sperm motility, and normal morphology reduced significantly after than before COVID-19 diagnosis.[4] A previous study by Sarier *et al.*[10] reported that the parameters in 594 patients who visited a urology clinic for infertility were not elevated, and semen quality was similar during the pandemic compared to the prepandemic values. Conversely, other studies did not find significant differences in semen volume, sperm count, or motility before and after COVID-19 diagnosis.[3,5,19]

Compared to the results of previous studies, our findings may be explained by the following reasons. First, the infected populations

Table 2: Comparison of semen parameters before and after SARS-CoV-2 infection in group A and group B

Parameter	*Normal value*	*Group A (n=109)*			*Group B (n=36)*		
		Baseline, median (IQR)	*Follow-up, median (IQR)*	*P*	*Baseline, median (IQR)*	*Follow-up, median (IQR)*	*P*
Abstinence period (day)	-	5.0 (4.0–6.0)	5.0 (4.0–6.5)	0.054	4.5 (4.0–6.0)	5.0 (4.3–6.0)	0.129
Volume (ml)	>1.5	3.0 (2.4–3.6)	3.0 (2.0–3.6)	0.542	3.0 (2.4–3.6)	3.2 (2.4–3.8)	0.170
Sperm concentration ($\times10^6$ ml^{-1})	>15	50.0 (32.0–63.0)	39.0 (28.0–60.0)	0.015	52.0 (36.5–69.8)	59.5 (41.5–70.3)	0.291
PR (%)	>32	44.0 (31.5–52.0)	37.0 (28.5–51.0)	0.027	50.5 (32.3–52.0)	52.0 (38.5–54.0)	0.065
PR + NP (%)	>40	56.0 (40.5–61.0)	46.0 (40.0–60.0)	0.031	58.5 (40.3–61.0)	60.5 (46.5–62.0)	0.061
TPRSC ($\times10^6$)	>7.2	56.7 (27.3–99.2)	36.5 (17.2–78.8)	0.035	78.5 (28.4–105.6)	95.4 (62.8–120.0)	0.136
TSC ($\times10^6$)	>39	148.8 (79.1–223.2)	111.0 (60.8–191.8)	0.056	156.0 (102.9–221.3)	194.7 (126.0–240.0)	0.153

Wilcoxon rank-sum test was used to compare before and after infection semen parameters. A two-tailed $P<0.05$ was considered statistically significant. Group A: volunteers who had semen analysis data within 90 days after SARS-CoV-2 infection; group B: volunteers who had semen analysis data on or after 90 days after SARS-CoV-2 infection. IQR: interquartile range; -: no value; PR: progressive motility; NP: non-PR; TPRSC: total PR sperm count; TSC: total sperm count; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

Table 3: Comparison of semen parameters before and after SARS-CoV-2 infection in group C and group D

Parameter	*Normal value*	*Group C (n=86)*			*Group D (n=23)*		
		Baseline, median (IQR)	*Follow-up, median (IQR)*	*P*	*Baseline, median (IQR)*	*Follow-up, median (IQR)*	*P*
Abstinence period (day)	-	5.0 (4.0–6.0)	5.0 (4.0–7.0)	0.107	4.0 (4.0–6.0)	5.0 (4.0–6.0)	0.313
Volume (ml)	>1.5	3.0 (2.4–3.6)	2.8 (2.0–3.6)	0.405	3.0 (2.5–4.6)	3.0 (2.8–4.0)	0.795
Sperm concentration ($\times10^6$ ml^{-1})	>15	51.0 (32.0–64.3)	45.0 (28.8–62.0)	0.081	45.0 (28.0–56.0)	32.0 (22.0–50.0)	0.048
PR (%)	>32	49.0 (30.8–52.0)	38.0 (30.0–52.0)	0.138	40.0 (32.0–51.0)	34.0 (26.0–38.0)	0.046
PR + NP (%)	>40	58.0 (41.0–62.0)	50.0 (40.0–60.0)	0.107	50.0 (40.0–60.0)	45.0 (36.0–50.0)	0.170
TPRSC ($\times10^6$)	>7.2	57.2 (24.4–101.7)	47.4 (16.5–84.2)	0.123	47.4 (27.7–94.5)	32.4 (17.6–51.7)	0.171
TSC ($\times10^6$)	>39	148.8 (77.4–217.8)	118.5 (54.0–203.7)	0.139	144.0 (84.0–230.4)	106.4 (66.0–163.2)	0.097

Wilcoxon rank sum test was used to compare before and after-infection semen parameters. A two-tailed $P<0.05$ was considered statistically significant. Group C: volunteers who had semen analysis data within 90 days after SARS-CoV-2 infection and completed the three-dose SARS-CoV-2 vaccination booster; group D: volunteers who had semen analysis data within 90 days after SARS-CoV-2 infection and not completed the three-dose SARS-CoV-2 vaccination booster. IQR: interquartile range; -: no value; PR: progressive motility; NP: non-PR; TPRSC: total PR sperm count; TSC: total sperm count; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

Table 4: Comparison of semen parameters before and after SARS-CoV-2 infection in group E and group F

Parameter	*Normal value*	*Group E (n=28)*			*Group F (n=8)*		
		Baseline, median (IQR)	*Follow-up, median (IQR)*	*P*	*Baseline, median (IQR)*	*Follow-up, median (IQR)*	*P*
Abstinence period (day)	-	4.5 (4.0–5.8)	5.5 (4.3–6.0)	0.072	4.5 (4.0–6.0)	5.0 (4.3–5.0)	0.748
Volume (ml)	>1.5	2.9 (2.4–3.3)	3.0 (2.4–3.6)	0.531	3.3 (2.6–4.9)	3.7 (3.0–6.2)	0.063
Sperm concentration ($\times10^6$ ml^{-1})	>15	54.5 (44.3–70.8)	59.5 (47.0–73.5)	0.589	48.5 (21.5–61.0)	56.0 (31.8–64.3)	0.161
PR (%)	>32	51.0 (33.3–52.8)	52.0 (41.0–54.0)	0.157	37.5 (27.3–51.5)	51.0 (34.5–53.8)	0.206
PR + NP (%)	>40	60.0 (42.3–61.0)	61.0 (49.0–62.0)	0.104	45.0 (36.3–56.0)	59.5 (44.0–65.0)	0.263
TPRSC ($\times10^6$)	>7.2	78.5 (32.8–105.6)	93.9 (50.7–128.4)	0.339	71.7 (19.8–113.5)	107.1 (68.9–118.0)	0.208
TSC ($\times10^6$)	>39	152.4 (106.1–205.2)	190.2 (120.0–243.8)	0.412	190.5 (68.9–237.0)	209.1 (156.2–236.1)	0.207

Wilcoxon rank-sum test was used to compare before and after infection semen parameters. A two-tailed $P<0.05$ was considered statistically significant. Group E: volunteers who had semen analysis data on or after 90 days after SARS-CoV-2 infection and completed the three-dose SARS-CoV-2 vaccination booster; group F: volunteers who had semen analysis data on or after 90 days after SARS-CoV-2 infection and not completed the three-dose SARS-CoV-2 vaccination booster. IQR: interquartile range; -: no value; PR: progressive motility; NP: non-PR; TPRSC: total PR sperm count; TSC: total sperm count; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

are ethnically diverse and react differently to the virus. Previous studies have focused mainly on foreign populations. Second, the timing of infection and the type of virus strains are different. Our study population was infected with SARS-CoV-2 in December 2022, which differed from the time of infection of the cases reported previously; also, the virus strains and virulence were different, and virus virulence decreased over time. Third, we studied the changes in semen quality before and after SARS-CoV-2 infection in the same population rather than in two similar populations, unlike those described previously. Comparatively speaking, the current study reflects the effect of SARS-CoV-2 infection on male semen quality relatively more accurately.

Some studies reported the effect of SARS-CoV-2 vaccination, and most did not find any statistical difference in the vaccination effect on semen parameters.[20,21] However, whether SARS-CoV-2 vaccination has a protective effect on semen quality has not been reported. Based on whether the SARS-CoV-2 three-dose inactivated vaccination booster was completed, we divided the population with normal sperm concentration before infection into two groups and observed the changes in the sperm parameters within 90 days of infection. Interestingly, the volunteers who completed the vaccine booster (n = 86) showed no significant differences in the semen parameters before and after infection. Conversely, the unvaccinated and noncompleted vaccine booster (n = 23) markedly decreased sperm concentration and PR after infection. According to our results, the sperm volunteers with normal sperm concentrations before SARS-CoV-2 infection showed a decline in semen parameters within 90 days of infection. However, this decrease was not significant in

men who had completed the SARS-CoV-2 inactivated vaccine booster relative to those who either were not vaccinated or did not complete the booster vaccine. Thus, it can be deduced that for volunteers with normal sperm concentrations before infection, completion of the three-dose booster vaccine may exert a protective effect on semen quality after infection. However, several studies and large sample sizes are required to prove this phenomenon.

The exact mechanisms by which SARS-CoV-2 may affect semen parameters are not yet fully understood.[22] Thus, it can be speculated that the virus affects the testicular cells responsible for sperm production, thereby decreasing sperm count and motility. Furthermore, systemic inflammation and oxidative stress may be associated with SARS-CoV-2 infection that contributes to these changes. Typically, SARS-CoV-2 infection is accompanied by febrile symptoms and acute illness with fever may affect sperm spermatogenesis for a limited period.[23] Moreover, SARS-CoV-2 invades host cells through angiotensin-converting enzyme II (ACE2) and causes multi-organ injury. Some studies categorized the testis as an organ with a high susceptibility to the virus. SARS-CoV-2-binding proteins, ACE2 and type II transmembrane serine protease (TMPRSS2), are highly expressed in the testis,[24–26] but whether these are co-expressed is yet to be elucidated.[27–29] Furthermore, studies on the effect of SARS-CoV-2 infection on semen parameters are limited. Notably, the long-term effects of SARS-CoV-2 infection on male fertility are unknown, necessitating additional investigation on the impact of the virus on the reproductive system.

Nevertheless, the current study has some limitations. First, the data were obtained by analyzing semen from volunteers at a sperm bank; thus, the quality of semen is not representative of that of the general population, causing selection bias. Second, we did not group the study population based on the symptoms of infection, presence or absence, degree, and duration of fever. Third, in this study, we only focused on the effect of the virus on sperm motility; some other basic parameters (such as DNA fragmentation, oxidative stress, morphology, *etc.*) had not been studied. Fourth, since only a few volunteers in our sperm bank who were not infected with SARS-CoV-2 during December 2022 and because our study had a prolonged duration, even fewer men were found to fulfill the criteria. Therefore, in this study, there was no control group that was not infected with SARS-CoV-2 during the same period. However, this is a relatively large sample size focused on the changes in sperm parameters before and after SARS-CoV-2 infection. The data consisted of controlled information of the same individual before and after infection collected on a case-by-case basis; also, short-term and up to 90 days postinfection effects were observed. The duration of the study encompasses the entire life cycle of the sperm. In addition, the protective effect of SARS-CoV-2 vaccine on male semen quality was confirmed statistically.

CONCLUSIONS

Volunteers with normal sperm concentration before infection showed decreased semen quality within 90 days after SARS-CoV-2 infection, and sperm concentration, PR, PR+NP, and TPRSC differed significantly from those pre-infection. Interestingly, semen quality regained preinfection levels after 90 days of infection. The completion of three doses of booster vaccine may exert a protective effect on semen quality after infection.

AUTHOR CONTRIBUTIONS

JLM and YG conducted the study design, funding application, and project supervision and management. WKH, XHS, and AQG carried out the semen analysis. WKH and QLZ collected and collated the data. LW performed the statistical analysis and drafted the manuscript. JLM revised the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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